DETAILED ACTION

This Office action is in response to the communication filed 2-24-11.

Claims 42-50, 52-56, 63, 75-77, 80 are pending in the instant application.

Claims 52-56 have been are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions.

Claims 42-50 63, 75-77 and 80 have been examined on their merits as set forth below.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-24-11 has been entered.

Response to Arguments and Amendments

Applicant's arguments with respect to claims 42-50 63, 75-77 and 80 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-50, 63, 75-77, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eldrup et al (WO 03/100017) (priority date May 24, 2002) and Baker et al (WO 2005/044976) (priority date 6-20-03), the combination further in view of Zinnen (US 2005/0203044) and Jiang et al (US 2006/0116331).

The claims are drawn to an isolated siRNA comprising two strands, both of which are from 19-25 nucleotides in length, wherein at least one strand comprises at least 80% nucleotides of the formula optionally comprising a 2'-sugar modification which is optionally a fluorine or a 2'-O-alkyl, and which strand further comprises at least 80% or

all of the nucleotide linkages are ribo-N3' -> P5' thiophosphoramidate linkages, and which 60% or the nucleobases in the oligonucleotide are optionally ribonucleobases, and which siRNA optionally further comprises one covalently conjugated lipid moiety on the 5' or 3' terminus, which lipid moiety is optionally an unsubstituted or substituted fatty acid, which is optionally substituted with fluorine, or which lipid is optionally a sterol or hydrocarbon, which lipid is optionally linked via a linker, and which siRNA is optionally directed to a HIV target gene, and modulates HIV gene expression.

Baker et al (WO 2005/044976) (priority date 6-20-03) teach siRNA comprising two strands, both of which are from 19-25 nucleotides in length, wherein at least one strand comprises 2'-sugar modifications which are optionally a fluorine or a 2'-O-alkyl, and which strand further comprises at least ribo-N3' -> P5' thiophosphoramidate linkages, and which 60% or the nucleobases in the oligonucleotide are optionally ribonucleobases, and which siRNA optionally further comprises one covalently conjugated lipid moiety, which is optionally an unsubstituted or substituted fatty acid or sterol or hydrocarbon, which is optionally linked via a linker (see entire document, esp. the abstract, 11, 15-16, 26, 33-34, 39-44, 49-57, 72, 80-87, claims 1-22, 37, 40).

Eldrup et al (WO 03/100017) teach siRNA comprising two strands, both of which are from 19-25 nucleotides in length, wherein at least one strand comprises 2'-sugar modifications which are optionally a fluorine or a 2'-O-alkyl, and which strand further comprises ribo-N3' -> P5' thiophosphoramidate linkages, and which 60% or the nucleobases in the oligonucleotide are optionally ribonucleobases, and which siRNA optionally further comprises one covalently conjugated lipid moiety, which is optionally

an unsubstituted or substituted fatty acid or sterol or hydrocarbon, which is optionally linked via a linker (see entire document, esp. the abstract, pages 5-9, 31-37, 39, 42, claims 1-29).

The primary references do not teach siRNA comprising 80% or all ribo-N3' -> P5' thiophosphoramidate linkages, nor the targeting and inhibiting of expression of HIV genes, nor fatty acids substituted with at least one fluorine.

Zinnen (US 2005/0203044) teaches oligonucleotides for silencing a target gene, comprising at least one nucleotide or optionally up to 80% nucleotides comprising thiophosphoramidate linkages and further comprising a 2'-fluoro or 2'-O-alkyl modifications, which oligonucleotides are optionally single stranded or double stranded, and which specifically inhibit expression of an endogenous mammalian or HIV target gene, optionally further comprise a covalently attached linker for the attachment of additional molecules to the termini of the silencing oligonucleotides (see entire document, esp. paragraphs 0004-5, 0012, 0053, 0065, 0074, 0082, 0087-102).

Jiang et al (US 2006/0116331) teach oligonucleotides with covalently conjugated lipid moieties, which lipids comprise fatty acids comprising at least one fluorine, and Jiang teaches the advantages of incorporating fluorines into fatty acids and conjugating them to oligonucleotides for enhancing amphiphilic molecules in their anti-HIV activity (see esp. paragraphs 0023-0035).

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to design and assess siRNA molecules comprising two strands between 19-25 nucleotides in length and further comprising 2'-sugar modifications

which are optionally a fluorine or a 2'-O-alkyl, and further comprising ribo-N3' -> P5' thiophosphoramidate linkages because the methods for introducing these modifications into siRNA and the advantages of incorporating these modifications into siRNA molecules were well known in the art, as taught previously by Baker and Eldrup. One would have been motivated to incorporate such modifications because they were well known to increase and stabilize target binding and target gene inhibition, as taught previously by Baker, Eldrup and Zinnen. One of skill in the art would have reasonably expected that including 80% of the linkages of single strand of the siRNA as ribo-N3' -> P5' thiophosphoramidate linkages, and including the 2'-O-modifications instantly claimed, would provide for siRNA with enhanced target binding, stability and inhibitory capabilities. It also would have been obvious to covalently link lipid moieties onto the termini of the siRNA, via a linker or directly, because the technology was well known in the art at the time of the instant invention, as taught previously by Baker, Eldrup and Zinnen, and one of skill in the art would have reasonably expected siRNA comprising these lipophilic moieties would have enhanced target cell binding and uptake.

It would also have been obvious to incorporate fluorines into fatty acids of lipid groups that are covalently linked to inhibitory oligonucleotides, including single and double stranded iRNA molecules because Jiang taught the methods to do this, and it was well known in the art that fluorocarbon group analogs have enhanced anti-HIV capabilities. One would have been motivated to design these fluorine containing inhibitory molecules as a means of enhancing the therapeutic efficacy of iRNA molecules that target HIV in subjects in need of such therapy. One would have

reasonably expected that the lipophilicity of inhibitory oligonucleotides would be enhanced by the conjugation of these fatty acid containing lipid moieties, enhancing cellular penetration, and that these oligonucleotides would provide better anti-HIV therapeutic effects because of enhanced cellular uptake and because of their cumulative anti-HIV and HIV inhibitory capacities.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time of filing.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** The examiner's office hours are generally Monday-Friday, 10:30am - 7pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita, can be reached on (571) 272-2876. Any inquiry of a general nature

or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
2-6-12

/Jane Zara/

Primary Examiner, Art Unit 1635